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Abstract: Patients with bilateral vestibular loss (BVL) experience oscillopsia during passive head movements,(1) e.g., walking or driving. Because their vestibulo-ocular reflex does not stabilize gaze with compensatory eye movements, patients with vestibular deficiency make refixation saccades to a target.(2) Some can trigger directionally accurate "covert" saccades during head movements and "overt" saccades afterward.(3) Covert saccades, with latencies as short as 70 milliseconds in unilateral vestibular loss,(3) reduce oscillopsia. To clarify the underlying mechanism, we investigated the sensory inputs required to evoke short-latency catch-up saccades.

DOI: https://doi.org/10.1212/WNL.0b013e3182a08d36

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ZORA URL: https://doi.org/10.5167/uzh-80074
Journal Article
Accepted Version

Originally published at:
Lehnen, N; Glasauer, S; Jahn, K; Weber, K P (2013). Head impulses in complete bilateral vestibular loss: Catch-up saccades require visual input. Neurology, 81(7):688-690.
DOI: https://doi.org/10.1212/WNL.0b013e3182a08d36

Head impulses in complete bilateral vestibular loss: catch-up saccades require visual input

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Count:	Title: 91 characters	Text: 837 words
	References: 7	Figures: 1

Study funding: The Betty and David Koetser Foundation for Brain Research, the German Federal Ministry of Education (Grant 01 EO 0901), and the Faculty of Medicine of the University of Munich.

Search terms: oscillopsia [197], neurootology [209], vestibulo-ocular reflex (VOR)

Contributions:

N.L. designed the study, analyzed and interpreted the data, conducted the statistical analysis, and drafted and revised the manuscript for intellectual content.

S.G. designed the study, interpreted the data, and revised the manuscript for intellectual content.

K.J. designed the study and revised the manuscript for intellectual content.

K.P.W. designed the study, analyzed and interpreted the data, conducted the statistical analysis, and revised the manuscript for intellectual content.

Disclosures:

Dr. Lehnen received speaker honoraria from Interacoustics and Autronic Reglersysteme and research support from the German Federal Ministry of Education and Research (BMBF), the Faculty of Medicine of the University of Munich, and the Friedrich-Baur-Foundation. She is a shareholder of EyeSeeTec GmbH.

Dr. Glasauer receives research support from the German Research Foundation (DFG) and the German Federal Ministry of Education and Research (BMBF) and served as a reviewer for the European Commission.

Dr. Jahn received travel expenses and honoraria for lectures from Abbott, Boehringer Ingelheim Pharma, and Medtronic. He receives research support from the German Research Foundation (DFG), German Federal Ministry of Education and Research (BMBF), and Biogen Idec.

Dr. Weber received funding for travel from GN Otometrics, acts as an unpaid consultant to GN Otometrics, received funding from (1) The Betty and David Koetser Foundation for Brain Research and (2) Forschungskredit of the University of Zurich.

Introduction

Patients with bilateral vestibular loss (BVL) experience oscillopsia during passive head movements[1], e.g., walking or driving. Because their vestibulo-ocular reflex (VOR) does not stabilize gaze with compensatory eye movements, patients with vestibular deficiency make re-fixation saccades to a target[2]. Some can trigger directionally accurate "covert" saccades during head movements and "overt" saccades afterwards[3]. Covert saccades, with latencies as short as 70ms in unilateral vestibular loss[3], reduce oscillopsia. To clarify the underlying mechanism, we investigated the sensory inputs required to evoke short-latency catch-up saccades.

Methods

Patients

Six patients with neurofibromatosis 2 (median age 44 years, range 39-61, two men) who had previously had surgery for bilateral vestibular Schwannoma participated. Five had no vestibular response to calorics, galvanic vestibular stimulation, or search-coil head impulse testing; one patient had residual hearing and vestibular function (horizontal head impulse velocity gain: right 0.15±0.02/left 0.06±0.04, mean±SD).

Standard Protocol Approvals, Registrations, and Patient Consents

All patients gave their written informed consent; the investigation was approved by the Ethics Committee of the Medical Faculty of Munich University and performed in accordance with the Declaration of Helsinki.

Head impulse testing

Horizontal head impulses, i.e., passive high-acceleration (2000-4000°/s^2), small-amplitude (10-20°) horizontal head rotations[2], were applied randomly while patients fixated a target

1.40m away. Impulses were given under two conditions: 1) in dim light with target permanently visible and 2) in darkness with target switched off at least 1s before impulse start. Two-dimensional eye and head positions were measured with the search-coil technique (140cm side-length cubic coil frame, Remmel Systems®)[4]. One search coil (Skalar®, Delft, Netherlands) was on the left eye conjunctiva (anesthetized with topical oxybuprocain), another on a wooden bite bar. Head and eye positions, and target on/off signal data were recorded at a rate of 1kHz.

Data analysis

Data were analyzed offline using custom MATLAB® software (Mathworks, Natick, USA)[3, 4]. Head impulse start was defined as the point when head velocity crossed 2% of peak head velocity. Impulses ended when head velocity crossed zero again. Saccades were detected as described elsewhere[5]. Saccade onset was at eye peak acceleration. Latency was the difference between head impulse start and first saccade onset. Minimal latency was the smallest first saccade latency for each subject. Cumulative saccade amplitude was determined as previously described[5]. Significance level was 0.05.

Results

Figure 1A shows head (top) and eye (bottom) velocity traces during head impulse testing in one patient with chronic complete BVL. With the target permanently visible (left), the patient generated frequent overt and covert catch-up saccades (arrow) to compensate for the deficient VOR. Minimal saccade latency was 79ms. Like all five patients with total BVL, the patient failed to produce catch-up saccades in darkness (right). Figure 1B shows normalized, summated amplitudes of their catch-up saccades in response to head impulses (shaded gray area) with (left) and without (right) permanently visible target. Cumulative saccade amplitude

was 3.8-fold higher with a permanent target (paired t-test, p=0.01). Minimal saccade latency in light ranged from 79-91ms (95% confidence interval: 77-90ms).

In contrast to total BVL patients, a patient with residual vestibular function (figure 1C) stabilized gaze with covert and overt catch-up saccades in light (left, minimal saccade latency 83ms) and darkness (right, 87ms). Mean first saccade latency in this patient in darkness (150ms) was not different from that of total BVL patients in light (149±12ms, mean±SD, t-test, $p>0.05$). SD of first saccade latency in darkness (28ms) was smaller than the SD of total BVL patients in light (53ms, Chi-square-test, $p<0.01$).

Discussion

Catch-up saccades following passive head impulses require visual input in complete BVL. In darkness, they are only possible with residual vestibular function. Proprioception alone is insufficient; otherwise they would also be possible in darkness. The same is true for anticipatory saccades. Moreover, anticipation would not elicit directionally accurate responses to passive and random stimuli.

Vision has not been considered a trigger for covert saccades because visually-induced saccades usually have longer latencies[6]. Our findings suggest there is an unknown neural mechanism for rapid visually-induced saccade generation. Visual-to-ocular motor processing with latencies of 80ms[7] has the prerequisites for such a mechanism.

Even small residual vestibular input can trigger re-fixation. This is important for the many patients with unilateral or incomplete vestibular deficiency. Previously, vestibular input was known to elicit short latency quick phases[6], but not directionally appropriate saccades.

Minimal and mean latency of purely vestibular-triggered saccades (incomplete BVL, darkness) did not differ from those of visually-triggered saccades in the total BVL group. This indicates a common underlying neural mechanism. Latency distribution was tighter with a smaller SD in purely vestibular-triggered than in visually-triggered saccades because visually-

triggered saccades also occurred late after the head movement to compensate for retinal error. No late saccades occurred for vestibular-triggered saccades in darkness.

Thus, visual input is crucial for compensation of BVL, but any residual vestibular function helps trigger short-latency catch-up saccades which reduce retinal slippage and distressing oscillopsia. Consequently total BVL patients can still generate covert saccades in light[5], but they evoke less covert saccades than those with unilateral disease[5]. These findings will improve counseling and rehabilitation of BVL patients.

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Figure legends

Figure 1: Catch-up saccades in complete bilateral vestibular loss require visual input.

A) Eye (inverted, bottom) in response to head (top) velocity during head impulse testing in a patient with complete bilateral vestibular loss (note the absent vestibulo-ocular reflex (VOR) response, arrow). In light (left), the patient-generated frequent catch-up saccades (arrow) to correct for the head movements (minimal saccade latency: 79ms). In darkness (right), there were no catch-up saccades (arrow).

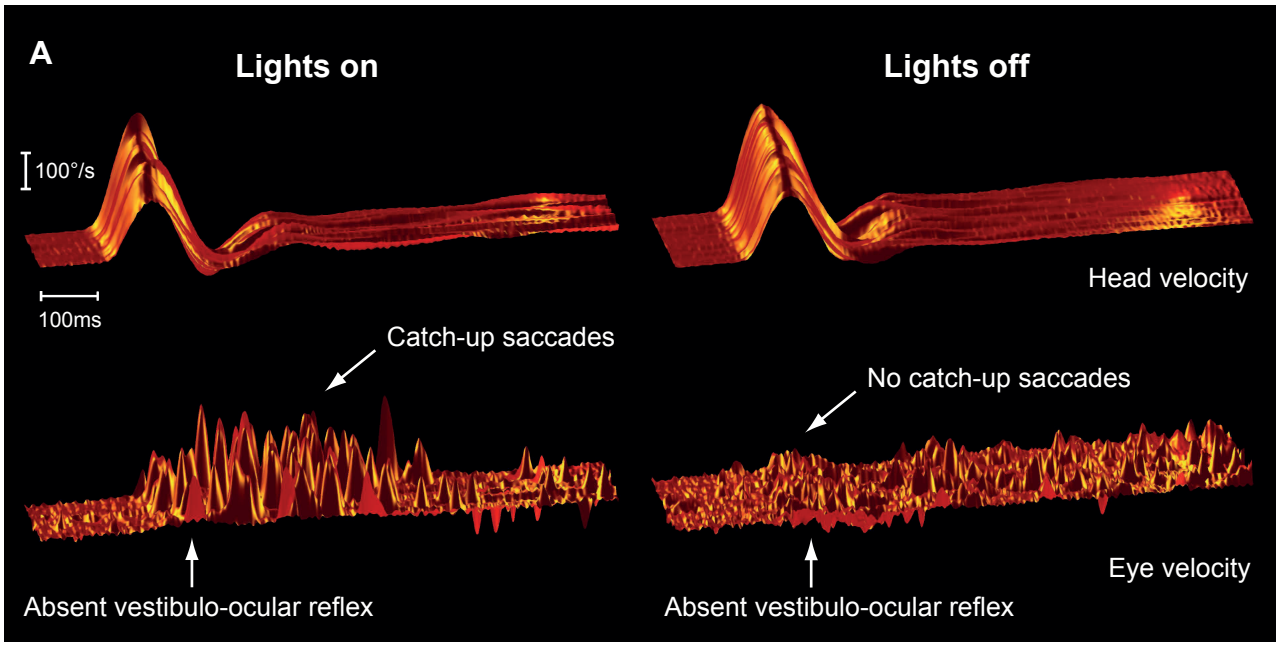
B) Cumulative catch-up saccade amplitude of all five patients with complete bilateral vestibular loss. Patients generated 3.8-fold larger cumulative amplitude of catch-up saccades (area under the curve) after head impulses in light (left) compared to darkness (right). Histogram bars represent summated amplitudes of catch-up saccades as a function of latency in 10-ms bins after head impulse onset. Saccade amplitude is adjusted relative to the number of head impulses per patient, and the normalized scale is kept in proportion between the "lights on" (left) and "lights off" condition (right). Gray gradients symbolize head movement during impulses.

C) Head impulse test in a patient with residual vestibular function (same depiction as in A; note the residual vestibulo-ocular reflex (arrows). The patient triggers appropriately directed catch-up saccades of similar latency during head impulses in light (left, minimal saccade latency 83ms) and in darkness (right, minimal saccade latency 87ms).

Acknowledgements

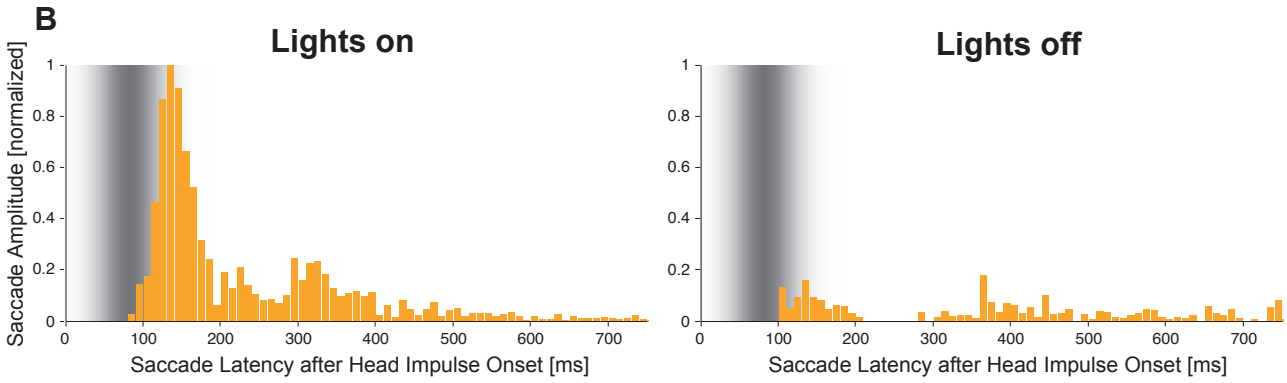
We thank Thomas Brandt for discussions and advice, Nicolas S. Todd for help with data analysis, and Judy Benson for copy-editing the manuscript. This research was supported by the Betty and David Koetser Foundation for Brain Research, the German Federal Ministry of Education (Grant 01 EO 0901), and the Faculty of Medicine of the University of Munich.

Patient with total bilateral vestibular loss



5 patients with total bilateral vestibular loss

Cumulative catch-up saccade amplitude



Patient with incomplete bilateral vestibular loss